R E M A R K S

Claim 43 was objected to for the reasons set forth in Item No. 9 on page 4 of the Office Action.

Claim 43 was amended into independent format by inclusion of the features of claim 40.

In reply to Item No. 10 near the bottom of page 4 of the Office Action, claim 58 was canceled.

In response to Item No. 11 bridging pages 4 and 5 of the Office Action, claim 59 was canceled.

With respect to Item No. 12 at the middle of page 5 of the Office Action, claim 66 was canceled.

Applicants are pleased to note that claim 65 was deemed to be allowable, as indicated in Item No. 13 on page 5 of the Office Action.

Claim 59 was rejected under 35 USC 112, second paragraph, for the reasons stated in Item No. 14 on page 5 of the Office Action.

As discussed hereinabove, claim 59 was canceled.

Claims 40 to 43, 45, 59 to 64 and 66 to 68 were rejected under 35 USC 112, first paragraph, for allegedly including new

matter, for the reasons set forth in Item No. 15 on page 6 of the Office Action.

The claims were amended to delete SEQ ID NO: 37 and SEQ ID NO: 38.

Claims 40 to 43, 45, 56 to 60, 62 to 64 and 66 were rejected under 35 USC 112, first paragraph, for alleged lack of written description, for the reasons stated in Item Nos. 15 and 16 on pages 6 and 7 of the Office Action.

Claims 40, 43 and 56 were amended to recite that the micro-organism which belongs to the *Penicillium* genus is selected from the group consisting of *Penicillium citrinum*, *Penicillium brevicompactum* and *Penicillium cyclopium*. These Penicillium species are supported in the paragraph at the middle of page 9 of the specification.

In view of the above, it is respectfully submitted that the presently examined claims comply with all the requirements of 35 USC 112.

The present claims concern a method for producing ML-236B. ML-236B is a HMG-CoA reductase inhibitor. Pravastatin is a HMG-CoA reductase inhibitor. The presently claimed method involves

culturing a *Penicillium* host cell (*Penicillium citrinum, Penicillium brevicompactum* or *Penicillium cyclopium*) which is transformed by a vector comprising a polynucleotide encoding a protein having the amino acid sequence of SEQ ID NO: 42.

Claims 40, 42, 43, 45, 60, 61, 63, 64, and 66 to 68 were rejected under 35 USc 103(a) as being obvious over Abe et al. (WO 01/12814), published February 22, 2001 (see IDS filed June 10, 2003) in view of Yu et al. (Applied and Environmental Microbiology, (1995) 61(6) : 2372-2377) for the reasons indicated in Item No. 17 on pages 7 to 9 of the Office Action.

It was admitted at the middle of page 8 of the Office Action that Abe et al. (WO 01/12814) do not expressly teach transforming host *Penicillium citrinum, Penicillium brevicompactum* and *Penicillium cyclopium* with each of the disclosed genes individually.

In WO 01/12814, a gene cluster was identified which could increase the production of ML-236B. Although one gene of the cluster was initially called "mlcR," the function of "mlcR" was not actually identified. The word "mclR" was a mere symbol in WO 01/12814, and there were no showing in WO 01/12814 that mclR

was a regulatory gene. Hence, a person of ordinary skill in the art would not be able to predict the function of mclR from WO 01/12814.

In Yu et al., the authors predicted the aflR gene of *Aspergillus flavus* from the aflR gene of *Aspergillus parasiticus* based on their homology. Actually, the overall homology of the above two aflR genes is 80 to 90% and a person of ordinary skill in the art could predict the regulatory function of one aflR gene from the other aflR gene. However, the aflR gene and the mlcR gene reveal no homology. Hence, a person of ordinary skill in the art would not be able to predict the regulatory function of the mlcR gene from the aflR gene.

In the present specification, the regulatory function of mlcR was disclosed for the first time (see Test Example 1 and Example 17). Accordingly, it is respectfully submitted that the regulatory function of the mlcR gene cannot be deduced straightforwardly on the basis of the disclosure in Yu et al. and/or WO 01/12814.

In Chang et al. (Applied and Environmental Microbiology, (1995), 61(6):2372-2377), the authors cultivated *Aspergillus*

parasticus in a minimal medium containing nitrate. It was known in the art that the production of aflatoxin was reduced in the presence of nitrate. Chang et al. indicate merely that the nitrate inhibition of the expressions of the genes (nor-1, ver-1 and omt-A) of the aflatoxin production pathway were relieved by the increased expression of aflR. Hence, Chang et al. do not teach whether the increased expression of aflR really improves the yield of aflatoxin in the absence of nitrate.

For testing functions of a specific gene, persons with ordinary skill in the art often cultivate microorganisms under the poor nutrient conditions as Chang et al. performed. On the other hand, such poor conditions are not appropriate to produce useful natural compounds in microorganisms. Hence, Chang et al. do not teach whether the increased expression of aflR really improves the yield of aflatoxin under the rich nutrient conditions used in Test Example 1 of the present specification.

Submitted concomitantly herewith is an INFORMATION DISCLOSURE STATEMENT which encloses a copy of Flaherty et al., Applied and Environment Microbiology, (1997), 63(10), 3995-4000.

Applicants have informed the undersigned that Flaherty et al. indicate that overexpression of aflR leads to increased production of aflatoxin in *Aspergillus flavus*. Flaherty et al. also cultivated microorganisms under nutrient poor conditions. The yield of aflatoxin was increased from 0.01 to 1 µg/ml to 1 to 50 µg/ml by the overexpression of aflR in Flaherty et al., and these yields are too low for commercial manufacture of natural compounds.

The aflR gene and the mlcR gene are totally different substances. Persons of ordinary skill in the art would not be able to actually predict the function of a specific gene solely by the knowledge of another gene having a different function in a different species (it is noted that aflatoxin and ML-236B are different compounds).

It is therefore respectfully submitted that applicants' claimed invention is not rendered obvious over the references, either singly or combined in the manner relied on in the Office Action in view of the many distinctions discussed hereinabove. It is furthermore submitted that there are no teachings in the

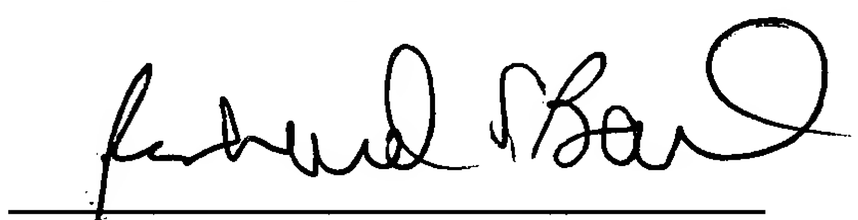
references to combine them in the manner relied on in the Office Action.

Reconsideration is requested. Allowance is solicited.

Enclosed is a check for $86 in payment of one additional independent claim.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Encs.: (1) INFORMATION DISCLOSURE STATEMENT

(2) Check for $86.00